

R E M A R K S

Claims 10 to 17 and 19 to 23 as presented with applicants' paper dated February 28, 2006, are currently pending in this application.

The Examiner reiterated the rejection of Claims 10 to 17 and 19 to 23 under Section 101 as being unpatentable over Claims 1 to 9 of US 6,482,772. It is respectfully requested that the respective issue be held in abeyance until the disclaimer which was filed by applicants in U.S. Patent 6,482,772 on February 26, 2004, has been approved and entered by the Certificate of Correction Branch. Favorable action is solicited.

Further, the Examiner rejected Claims 11 to 17 and 19 to 22 under 35 U.S.C. §112, ¶2, as being indefinite. In particular, the Examiner argued that the meaning of the term "alkylpolyglycoside" and the meaning of a degree of polymerization of 1 was unclear. Favorable reconsideration of the Examiner's position and withdrawal of the rejection is respectfully solicited in light of the following and the enclosed copy of *H. Mollet*, Formulation Technology, Wiley-VCH 2004, page 34.

The "distinctly claim" requirement of 35 U.S.C. §112, ¶2, means that the claims must have a clear and definite meaning when construed in the light of the complete patent document,¹⁾ and the test of definiteness is whether a person of ordinary skill in the pertinent art would understand the bounds of the claim when reading it in the light of the supporting specification.²⁾ As explained by the Board in *Ex parte Wu*³⁾

In rejecting a claim under the second paragraph of 35 U.S.C. 112, it is incumbent on the examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with reasonable degree of precision and particularity the particular area set out and circumscribed by the claims.

Additionally, it is well settled that an application need not teach,

1) *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 227 USPQ 293 (Fed. Cir. 1985)

2) *Morton Int. Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 28 USPQ2d 1190 (Fed. Cir. 1993); *Orthokinetics Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 USPQ2d 1081 (Fed. Cir. 1986)

3) 10 USPQ2d 2031 at 2033 (BPAI 1989).

and preferably omits, that which is well known in the art.⁴⁾

Applicants have addressed the meaning of the term "alkylpolyglycoside" (*in the following also referred to as "APG"*) on page 13, indicated line 1 et seq., of the application, and the exemplary commercially available products which are mentioned in that context corroborate that the respective class of substances is well known in the art. A corresponding summary of the technical background knowledge regarding the nature of **APGs** and their degree of polymerization is, for example, also found in col. 2, indicated line 32, to col. 3, indicated line 45, of **Garst et al.** (US 5,550,115).⁵⁾ It is evident from the technical background which is summarized not only by applicants but also by **Garst et al.** that a person of ordinary skill in the pertinent art is well aware of the meaning of the term "alkylpolyglycoside" and the meaning of a degree of polymerization of 1 of **APGs**. Further and for the Examiner's convenience applicants have enclosed herewith a formula representation of a group of **APGs** in figure 1.28 on page 34 of **Mollet**.

The foregoing and the attached corroborate that a person of ordinary skill in the pertinent art is fully apprised of the meaning of the term "alkylpolyglycoside" and of the meaning of "a degree of polymerization of 1" in the context of **APGs** so that the respective expressions cannot be deemed to render the subject matter of applicants' claims indefinite within the meaning of Section 112, ¶2. It is therefore respectfully requested that the rejection be withdrawn. Favorable action is solicited.

Additionally, the Examiner rejected Claims 10 to 17 and 19 to 23 under 35 U.S.C. §112, ¶1, as lacking an enabling disclosure regarding sulfonyl urea herbicides beyond the representative employed in applicants' Example 16 on page 32 of the application. The Examiner asserted in particular that a person of ordinary skill in the art could not practice the invention without undue experimentation

- 1) because the pertinent art lacked predictability;
- 2) because the application failed to provide guidance as to how to use the invention successfully with all sulfonyl urea herbicides; and

4) *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

5) U.S. counterpart of **WO 95/28410** mentioned on page 2, indicated lines 25 and 26, of the application.

- 3) because the application failed to contain working examples to support all sulfonyl urea herbicides.

Applicants' invention pertains to a particular solid mixture which comprises, on the one hand, a sulfonyl urea herbicide⁶⁾ and, on the other hand, an **APG**,⁷⁾ and to a method of controlling undesirable plant growth which involves the application of the solid mixture to such growth or an area where such growth occurs. In order to "make and/or use", or to practice, the invention which is defined in applicants' claims a person of ordinary skill in the art therefore has to be enabled

- (a) to provide the particular components of applicants' solid mixture,
- (b) to combine the respective components to form the solid mixture, and
- (c) to apply the solid mixture to the undesired plants or their environment.

The capabilities which are required for (b) combining the necessary components, and/or for (c) treating certain targets or locations with the requisite mixture, are deemed to be clearly well within the ordinary skill of a person in the herbicidal art. As noted above, an application need not teach and preferably omits that what is well known in the art,⁸⁾ so that applicants disclosure of the invention does not need to address these issues in order to meet the enablement requirement of Section 112, ¶1. The question whether applicants' disclosure is sufficient to enable a person of ordinary skill in the art therefore focuses on whether applicants provide a sufficient amount of information with regard to the mandatory constituents of the solid mixture and in particular, in light of the Examiner's remarks, sufficient information pertaining to sulfonyl urea herbicides.

The sulfonyl urea herbicides are addressed on pages 3 to 12 of the application. Moreover, the class of sulfonyl urea herbicides, including the particular herbicidal property of the representatives

6) Cf. e.g. page 3, indicated line 13, to page 12, indicated line 47, of the application.

7) Cf. e.g. page 13, indicated line 1, to page 14, indicated line 22, of the application.

8) *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986); *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Cf. also applicants' remarks on pages 21 to 23 of the application.

of this class, is well known in the art. This fact is, for example, corroborated by the enclosed copy of *K. Hirai* in P. Böger et al. (editors), "Herbicide Classes in Development," Springer-Verlag Berlin Heidelberg 2002, pp. 180-196. Given the technical background knowledge of a person having ordinary skill in the pertinent technology it is not apparent to applicants why such a person of ordinary skill would be required to engage in more than routine experimentation in order to select any one of the known sulfonyl urea herbicides and to combine it with an *APG* to form the solid mixture, particularly since "[t]he solid formulations according to the invention can be prepared by various processes known to the person skilled in the art."⁹⁾ More particularly, given the background knowledge pertaining to sulfonyl urea herbicides it is not apparent to applicants how the pertinent art can reasonably be deemed to be "unpredictable" in that regard. The Examiner's respective position is, therefore, not understood.

The Examiner relied with regard to (2) on the Court's holding in *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940) that: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result."¹⁰⁾ However, sulfonyl urea herbicides clearly cannot reasonably be considered to be "*chemicals and chemical compounds, which differ radically in their properties.*" Also, applicants' disclosure on pages 3 to 12 clearly provides the requisite "enumeration of a sufficient number of the members of a group or by appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result" referenced by the Court. The respective holding is accordingly not suited to support the Examiner's position. Further, as noted above, "[t]he solid formulations according to the invention can be prepared by various processes known to the person skilled in the art"¹¹⁾ so that the making and using of applicants' invention clearly does not require "ingenuity beyond that to be expected of one of ordinary skill" as the Examiner would have it.¹²⁾ It is also noted

9) Page 21, indicated lines 42 and 43, of the application.

10) Office action page 5, subsection 3, lines 3 to 7.

11) Ibid.

12) Office action paragraph bridging pages 5 and 6.

that the Examiner has not pointed to any statement made by applicants which is, on its face, contrary to generally accepted scientific principles.¹³⁾ The Examiner's findings regarding the sufficiency of the guidance which applicants' presented in the application is, therefore, clearly in error.

As noted in the foregoing, a person of ordinary skill in the art does not require guidance or direction beyond the information provided in applicants' disclosure of the invention

- (a) to provide a particular sulfonyl urea herbicide of applicants' solid mixture,
- (b) to combine the respective sulfonyl urea herbicide with an **APG** to form the solid mixture, and
- (c) to apply the solid mixture to the undesired plants or their environment.

The Examiner's position that a person of ordinary skill in the art would require working examples to support all sulfonyl urea herbicides is, therefore, clearly without merit.

It is well settled that an assertion by the PTO that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating those doubts.¹⁴⁾

... it is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.[¹⁵⁾]

In light of the foregoing remarks it is respectfully urged that the Examiner has not presented any such acceptable evidence or reasoning. It is therefore respectfully urged that the rejection of Claims 10 to 17 and 19 to 23 under Section 112, ¶1, be withdrawn. Favorable action is solicited.

13) Ibid.

14) *In re Dinh-Nguyen*, 492 F.2d 856, 858, 181 USPQ 47, 49 (CCPA 1974); *In re Bowen*, 492 F.2d 859, 862, 181 USPQ 48, 51 (CCPA 1974); *In re Armbruster*, 512 F.2d 676, 185 USPQ 152 (CCPA 1975).

15) *In re Marzocchi*, 439 F.2d 220, 222-23, 169 USPQ 367, 369-70 (CCPA 1971); footnote and citations omitted.

Last but not least the Examiner rejected Claims 10 to 17 and 19 to 23 under 35 U.S.C. §103(a) as being unpatentable in light of the teaching of *Kocur et al.* (US 5,258,358). The Examiner asserted in this context that the reference teaches a combination of a sulfonyl urea herbicide with an *APG*, albeit in liquid form, and argued that the reference would have motivated a person of ordinary skill to turn away from the liquid formulations to a solid mixture. For the following reasons, applicants respectfully disagree.

The teaching of *Kocur et al.* relates to a particular formulation of glyfosinate-ammonium,¹⁶⁾ ie. a herbicide which is structurally unrelated to sulfonyl urea herbicides. The teaching specifically seeks to address problems which are associated with liquid formulations of glyfosinate-ammonium¹⁷⁾ such as phase separation which occurs where the formulations are free of organic solvents,¹⁸⁾ and the specific stability issues which are encountered upon storage at low temperatures.¹⁹⁾ According to the authors the respective problems are obviated by providing the liquid composition which comprises glyfosinate-ammonium in combination with a surfactant from the series of *APGs* and optionally further in mixture with certain fatty alcohol polyglycol ether sulfates, alkyldimethylamine oxides, alkyldimethylammonium chloride and/or coconut alkyldimethylammoniumacetic acid.²⁰⁾ It is clear from the referenced sections of the teaching of *Kocur et al.* that the particular and advantageous effects which are described are solely exhibited by the liquid preparations since phase separation as well as the storage problems which are described in the reference are specific to such formulations and the respective problems are not encountered in solid formulations. It should also be noted that the formulation problems are specifically associated with the particular type of active ingredient, namely glyfosinate-ammonium, which is, as noted, structurally unrelated to sulfonyl urea herbicides.

With a particular view to information which pertains to sulfonyl urea herbicides the reference merely remarks that the liquid compositions of glyfosinate-ammonium and the surfactant(s) may comprise other herbicidal substances which can enhance the effectivity of gly-

16) Cf. col. 1, indicated lines 8 to 15, of US 5,258,358.

17) E.g. col. 1, indicated lines 27 to 33 and 44 to 58, of US 5,258,358.

18) E.g. col. 1, indicated lines 27 to 33, of US 5,258,358.

19) E.g. col. 1, indicated lines 44 to 58, of US 5,258,358.

20) E.g. col. 1, indicated line 65, to col. 2, indicated line 9, of US 5,258,358.

fosinate-ammonium, and enumerates among other herbicides four representatives from the class of sulfonyl urea herbicides.

The Examiner's position that the reference would have motivated a person of ordinary skill in the art to turn away from the liquid formulations addressed in the reference to a solid formulation is not deemed to be well taken. As noted, the particular advantages are, according to *Kocur et al.*'s teaching, dependent on the fact that the formulation is in liquid form. This means that a person of ordinary skill in the art cannot reasonably expect to arrive at any advantageous effects if the formulation is in solid form instead of the liquid form which is mandated by the reference. There is, accordingly, no reason why a person of ordinary skill in the art would modify the teaching of *Kocur et al.* in a manner such that glyphosate-ammonium and the surfactant(s) and optionally one or more of the other herbicidal substances are formulated in solid rather than liquid form. The mere fact that the prior art may be modified in some manner so as to result in the invention as claimed does not make such a modification obvious unless the prior art suggests the desirability of such a modification.²¹⁾ The modification in question is, where applicants' invention and the teaching of *Kocur et al.* are concerned, clearly not suggested as a desirable modification and the respective modification can, therefore, clearly not be deemed to be rendered obvious by the reference. For this reason alone, the Examiner's rejection is deemed to be in error.

Additionally, the inventive subject matter as a whole which is referenced in Section 103(a) includes not only the elements which are recited in the claims, but also encompasses the properties and results which are inherent in the combination of the recited elements which are disclosed in the specification.²²⁾ Applicants have found that the use of **APGs** in solid formulations of sulfonyl urea herbicides results in a pronounced stabilization of the active ingredient in comparison to other wetting agents such as ethoxylated fatty amines or alcohol ethoxylate, and that this effect can be observed especially when water-soluble inorganic salts are present.²³⁾ The

21) Cf. *In re Fritch*, 972 F.2d 1260, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992); *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984); *Berghauser v. Dann*, Comr. Pats., 204 USPQ 393 (DCDC 1979); *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 221 USPQ 929 (Fed. Cir. 1984).

22) *In re Antonie*, 559 F.2d 618, 620, 195 USPQ 6, 8 (CCPA 1977).

23) Note e.g. page 2, indicated line 42, to page 3, indicated line 3, of the application.

teaching of *Kocur et al.* not only fails to render a solid formulation obvious within the meaning of Section 103(a). The reference also fails to suggest or imply that the combination of a sulfonyl urea herbicide with an **APG** in a solid formulation may have any effect on the stability of the sulfonyl urea herbicide. As explained in the foregoing, all of the advantageous properties which *Kocur et al.* attribute to the use of **APGs** pertain to the herbicide glyfosinate-ammonium and to liquid preparations thereof. As such, the reference fails to suggest or imply that **APGs** may exhibit any particular properties in a solid formulation and also fails to suggest or imply that the presence of an **APG** may have any effect on a sulfonyl urea herbicide, be it in a liquid or a solid formulation. Bearing in mind that obviousness cannot be predicated on what is not known at the time an invention is made even if the inherence of a certain feature is later established,²⁴⁾ and that it constitutes hindsight when one of ordinary skill in the art is imbued with the knowledge of the invention when the prior art reference fails to convey or suggest that knowledge,²⁵⁾ the teaching of *Kocur et al.* can clearly not be considered to render applicants' invention as a whole obvious within the meaning of Section 103(a).

The foregoing explanations show that the reference upon which the Examiner relied in rejecting applicants' claims under Section 103(a) is not sufficient to establish a *prima facie* case of obviousness. It is therefore respectfully requested that the rejection be withdrawn. Favorable action is solicited.

Moreover, in light of the foregoing and the attached, the subject matter defined in in applicants' claims is deemed to be patentable under the provisions of Sections 103(a) and 112, ¶1 and ¶2, of the Patent Act, and the application should therefore be in condition for allowance. Favorable action by the Examiner is respectfully solicited.

24) *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993); *In re Adams*, 356 F.2d 998, 148 USPQ 742 (CCPA 1966).

25) *Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 230 USPQ 303 (Fed. Cir. 1983).

Hans Mollet, Arnold Grubenmann

Formulation Technology

Emulsions, Suspensions, Solid Forms

Translated by H. R. Payne

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Preface

What do we mean by formulation technology? It has long been established as something of a discipline, the oldest formulation development and application in the pharmaceutical and chemical industries. In other words, it is a technology amongst a complex of technologies, including considerable economic aspects, cosmetics, and a wide range of formulation technologies, although admittedly not always recognized as such.

A large proportion of the products of formulation technology are synthetic, must be produced in large quantities, for agriculture, food, and medicine. They are often mixtures of many substances, pure dye substances, simple substances, and complex substances. In addition, they must be of the appropriate quality, and of the appropriate formulation into a product, freeflowing, dust-free, stable, concentrated, or as a product, slow-releasing.

It has long been known that many substances formulated can be formulated in a way that allows solubilization, dispersion, or emulsification, and can be formulated, although with some improvements, as a competitive product. Its competitiveness is determined by its formulation, its stability, and its formulation to flow.

The art of formulation is a multidisciplinary character, chemistry, analysis, and technology. It is a modern analytical formulation technology, and its empirical character is increasing. Its creativity and innovation are the creation of new

Biotensides are four to five times more expensive than ordinary tensides. Usually, however, they have a greater specific efficacy, so the cost of their use is reduced. An alternative to biotensides, in terms of their biodegradability, is offered by tensides derived from saccharides: *sorbitan fatty acid esters*, *saccharose fatty acid esters*, and *fatty alcohol polyglycosides*. Henkel has recently started producing *alkyl polyglucosides* commercially (Figure 1.28).

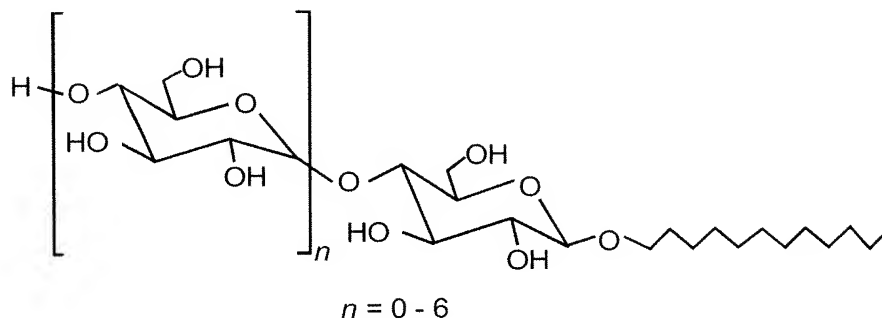


Figure 1.28. A new class of tensides: alkyl polyglucosides (APG), synthesized from fatty alcohols (8–14 C) and glucose. Advantages: excellent cleaning action and skin compatibility (no R38 notice), biodegradable.

Another class of tensides is the *glucamines*. Paraffinsulfonic acid glucamine salt is skin-compatible and is not an eye irritant. According to Hüls, the topic of mono-saccharide-based tensides is far from exhausted.

Reduction of tenside concentration by synergy: Certain tenside combinations are effective at lower concentration than either tenside alone, for example a fatty alcohol ether sulfate and a linear alkyl sulfate.

1.6 Cohesion, Adhesion, and Spreading

These phenomena of interface chemistry play a decisive role in wetting, rewetting, washing, and cleaning. Formulation chemists therefore need to have good knowledge of them.

1.6.1 Cohesion in a Liquid

Cohesion in a liquid is a measure of the attraction between similar molecules (A and A); *adhesion* is a measure of that between dissimilar molecules (A and B).

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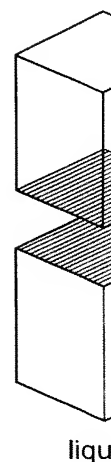


Figure 1.2

1.6.2 Sp

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Peter Böger · Ko Wakabayashi · Kenji Hirai (Eds.)

Herbicide Classes in Development

Mode of Action, Targets,
Genetic Engineering, Chemistry

With 96 Figures, 2 in Color, and 53 Tables

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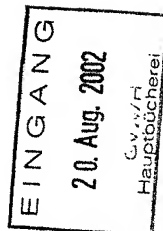


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Preface

Chemical pest control is in use in practically every country in the world since agrochemicals play a decisive role in ensuring food supply and protection against damage by pests, insects and pathogenic fungi. Particularly in the half-century since World War II, food production has risen dramatically in most parts of the world. In the last 20 years, the yield of major crops has roughly doubled in Western agriculture and there is still the potential for further achievements, particularly in the developing countries.

The world's cereal and rice production, now more than 2 billion tons/year, has to increase by 2.4% annually to cope with the rising food demand caused mainly by the growing population and improvement of living standards in most of the developing countries. Such a demand for food has to be achieved by higher yields from the restricted arable land already in use. Global farmland resources are about 1.4 billion ha, of which 1.2 billion ha is cultivated with major crops. Experts agree that a future substantial addition of new productive areas is unlikely. Those with a high yield potential are already in use; new fields with a lower output may possibly be obtained by cultivation of arid or cold areas. More recently, new areas of large-scale farmland have been developed in tropical regions of Latin America, primarily in Argentina and Brazil, at the cost of the destruction of tropical rain forest.

The 1980s were an exciting period for the development of modern herbicides, for both industry and academia. Acetolactate synthase (ALS) inhibitors, represented by the sulfonylurea (SU) and imidazolinone (IMI) classes, were introduced into chemical weed control. The start of the widespread use of new acetyl-CoA carboxylase (ACCase) inhibitors such as the phenoxypropionate and cyclohexanedione classes brought about a major turning point in the subsequent evolution of agrochemicals. The discovery of fluoromethyl tetrahydrophthalimides as PPO (= protoporphyrinogen oxidase, Protopx) inhibitors, such as flumiclorac-pentyl, is another breakthrough in the explosive development of the next-generation of cyclic imide classes. These new herbicide chemistries, which combine excellent activity with unparalleled lower dosage, crop safety, specific mechanism of action and/or structural high novelty, have been rapidly adopted worldwide and have had an amazing impact on agriculture.

Today, the use rate of modern herbicides is in the range of 100-300 g a.i./ha, with a declining tendency. In particular, the very low use rates of original SU and cyclic imide herbicides have prompted agrochemical researchers to find

classes derived from sulfonylureas are also ALS inhibitors. Group B of the HRAC classification includes 50 kinds of ALS inhibitors. All ALS inhibitors disclosed since 1990 are documented in this chapter and classified by their chemical structure, although some of them are not regarded as ALS inhibitors. Also, agricultural properties and several major synthetic routes of practical ALS inhibitors are briefly summarized. Moreover, the structural evolution of each class is chronologically reviewed relating to their chemical structures.

10.2.1

Sulfonylurea Acetolactate Synthase Inhibitors

The most important key to the market launch of sulfonylurea herbicides was the discovery of chlorsulfuron and sulfometuron-methyl by DuPont in the early 1980s, since then, 27 compounds have been commercialized and 3 compounds are under development. These practical sulfonylureas are shown in Table 1. Sulfonylureas have been subjected to structural modifications in order to reduce the dosage dramatically, widen the weed spectrum and enhance selectivity for crops. Hence, modern sulfonylureas exhibit extremely strong activity against numerous weeds, including grass and broadleaf weeds, and have played important roles in increasing the yield of primary crops such as rice, wheat, barley, soybeans, corn and so on. Additionally, some sulfonylureas such as metsulfuron-methyl are also used in non-crops.

10.2.1.1

Practical Sulfonylurea Acetolactate Synthase Inhibitors

Chlorsulfuron was the first sulfonylurea class ALS inhibitor to be commercialized by DuPont in 1984. It consists of a 2-chlorophenylsulfonyl group and a 4,6-disubstituted triazine ring, which are connected together through the urea moiety. Chlorsulfuron is the origin of the term of "sulfonylurea". Since the discovery of chlorsulfuron, explosive developments of the sulfonylurea class have been carried out by many companies. Chlorsulfuron has good selectivity for wheat, barley, oats and rye and shows good herbicidal activity against broadleaf weeds at as low as 4–30 g/ha with pre- or post-emergence application. Moreover, it controls different varieties of grass weeds and the water hyacinth. In particular, chlorsulfuron plays a most important role in spring wheat in North America by controlling harmful broadleaf weeds at rates of 20–30 g/ha by post-emergence application. Since the discovery of chlorsulfuron, introduction of a variety of substituents at the benzene and triazine rings has been actively accomplished because a slight difference in the chemical structure considerably affects herbicidal activity and crop safety.

Metsulfuron-methyl bearing a methoxycarbonyl group at the *ortho*-position of the benzene ring has been used as either a pre- or post-emergence herbicide at 2–8 g/ha in wheat, barley, oats and turf. It controls a wide range of annual and perennial broadleaf weeds. The herbicide is superior to

Table 1. Practical sulfonylurea ALS inhibitors

Chemical structure	ISO name Code No. Company	Dose Appl. method Target crops	Patent No.
<Sulfonylureas with triazine ring>			
	chlorsulfuron DPX-W-4189/DuPont (R ¹ =Cl, R ² =MeO, R ³ =Me)	4–30 g/ha pre, post cereals, turf	US4127405
	metsulfuron-methyl DPX-6376/DuPont (R ¹ =MeOOC, R ² =MeO, R ³ =Me)	2–8 g/ha pre, post non-crop, cereals	US4370480
	triasulfuron CGA-131036/Ciba-Geigy (R ¹ =Cl(CH ₃) ₂ O, R ² =MeO, R ³ =Me)	5–15 g/ha pre, post cereals	US4514212 EP44808
	ethamsulfuron-methyl DPX-A-7881/DuPont (R ¹ =MeOOC, R ² =EtO, R ³ =MeNH)	10–120 g/ha pre, post rice, rape, turf	EP136061
	cinosulfuron CGA-142264, CG-148 Ciba-Geigy (R ¹ =MeO(CH ₂) ₂ O, R ² =R ³ =MeO)	10–40 g/ha post rape	US4479821 EP44807
	proflsulfuron CGA-152005, CG-205 Ciba-Geigy (R ¹ =CF ₃ (CH ₃) ₂ , R ² =MeO, R ³ =Me)	12–40 g/ha post maize, turf, corn	EP120814
	tritosulfuron BASF (R ¹ =R ² =CF ₃ , R ³ =MeO)		DE4038430
	tribenuron-methyl DPX-L-5300, DPX-53 DuPont	5–30 g/ha post cereals, citrus	WO88/02599
	triflusaluron-methyl DPX-66037 DuPont	10–25 g/ha post sugar beet	WO89/0214
	iodosulfuron-methyl-sodium AE F11-5008 AgriEvo	post cereals	DE19520839 WO92/13845
<Sulfonylureas with pyrimidine ring>			
	sulfometuron-methyl DPX-T-F-5648, MfB-13/DuPont (R ¹ =R ² =R ³ =Me)	70–840 g/ha pre, post non-crop, turf	US4127405
	chlorsulfuron-ethyl DPX-F-6025, DPX-25/DuPont (R ¹ =Et, R ² =MeO, R ³ =Cl)	9–13 g/ha pre, post soybeans, turf	US4394506 US4547215
	primisulfuron-methyl CGA-136872/Ciba-Geigy (R ¹ =Me, R ² =R ³ =CHF ₂)	20–40 g/ha post soybeans, maize	EP84020 EP8478635
	oxasulfuron CGA-277476/Novartis (R ¹ =3-oxoethyl, R ² =R ³ =Me)	45–80 g/ha post soybeans	EP496701 US5209771

Table 1. Continued

Chemical structure	ISO name Code No. Company	Dose Appl. method Target crops	Patent No.
<Sulfonylureas with pyrimidine ring>			
	foramsulfuron Hoechst-Schering-AgrEvo (R=Me, X=OHCNH) mesosulfuron Hoechst-Schering-AgrEvo (R=MeO, X=MeSO ₂ NHCH ₃)		DE4335297 DE4415049
<Pyridylsulfonyleureas>			
	nicosulfuron DPX-V-9360/DuPont (R=Me, X=CO) rimisulfuron DPX-E-9636/DuPont (R=EtSO ₂) flazasulfuron SL-160, OK-116/Kshihara (R=CF ₃) trifloxysulfuron CGA-292230/Novartis (R=CF ₃ CH ₂ O) flupysulfuron-methyl-Na DPX-KE-459, IN-KE-459, JE-183/DuPont	40-60 g/ha post maize 5-15 g/ha post corn, turf, potatoes 25-100 g/ha post sugarcane, turf cereals 10 g/ha post soybeans, cereals	US4789393 WO9005728 EP3411011 WO94/23063 WO92/16522 WO8804297 EP327251 EP502740
<Sulfonylureas with heterocycles>			
	thifensulfuron-methyl DPX-M-6316, DPX-16 DuPont	17-35 g/ha post wheat, barley, citrus, soybeans	US4484029
	pyrazosulfuron-ethyl NCA-256, NC-311/Nissan (R=Et, X=H) halosulfuron-methyl NC-319/Nissan (R=Me, X=Cl)	14-30 g/ha pre, post rice, turf 70-140 g/ha, pre 18-35 g/ha, post corn, turf, sugarcane	JP0656792 JP60208977
	azimsulfuron DPX-A-8947, DPX-47 DuPont	8-20 g/ha post rice	US4746353 US4786311
	imazosulfuron TH-913/Takeda (X=Cl) sulfosulfuron MOX-37500, TKM-19 Takeda (X=EtSO ₂)	75-100 g/ha pre, post rice, turf 10-30 g/ha post cereals	JP6438091 JP05-9102 EP477808

Table 1. Continued

Chemical structure	ISO name Code No. Company	Dose Appl. method Target crops	Patent No.
<Benzyl-, Anilino- and Phenoxy-sulfonylureas>			
	bensulfuron-methyl DPX-F-5384, DPX-84/DuPont (R=MeOOC, X=CH ₃) cyclosulfuron AC-322140, AC-140/ACC (R=c-PrCO, X=NH)	20-100 g/ha pre, post rice 25-60 g/ha pre, post rice, cereals, turf	US4420325 US5009699 EP613618 WO92/00952
<Sulfonamidosulfonylureas>			
	ethoxysulfuron Hoe-095404, Hoe-404/AgriEvo (R=EtO, X=O) amidosulfuron Hoe-032 Hoechst	10-120 g/ha pre, post rice, cereals, turf 15-60 g/ha post cereals	EP342569 EP507093 EP560178 EP298901

chlorsulfuron in controlling violets and turfed knotweeds except for activities against catchweed bedstraw. Ciba-Geigy's sulfonylurea, triasulfuron was developed as a wheat and barley herbicide. It shows excellent herbicidal activity against *Apera spica-venti* and some *Lolium* sp., violets, catchweed bedstraw and broadleaf weeds at 5-15 g/ha with pre- or post-emergence application. Ethamsulfuron-methyl having a 6-ethoxy-4-methylamino-1,3,5-triazine ring was launched in 1993 by DuPont as an oilseed rape herbicide. Pre- and post-emergence treatment provides good herbicidal activity at 10-40 g/ha in spring rape and 80-120 g/ha in winter rape. It controls important weeds such as wild chamomile, henbit, ladythumb, wild mustard, common purslane, common chickweed and *Polygonum tomentosum*. Cinosulfuron was developed as a post-emergence herbicide. It shows strong activity against annual and perennial weeds including needle spikerush, Japanese bulrush, *Sagittaria pygmaea*, *Alisma canaliculatum* and *Cyperus serotinus* except for barnyard grass at 10-40 g/ha in transplanted and direct seeded rice. Prosulfuron was commercialized as a post-emergence corn herbicide. It is effective against broadleaf weeds such as velvetleaf, common lambsquarters, common purslane, common cocklebur, common ragweed and morningglory at rates of 12-40 g/ha. Triflurosulfuron is characterized by two trifluoromethyl groups at the 2- and 6-positions of the benzene and triazine rings, respectively. It is currently developed by BASF.

Tribenuron-methyl is a unique sulfonylurea substituted with a methyl group at the ureido-nitrogen atom. It was launched as a post-emergence herbicide in wheat. It is active on various kinds of perennial broadleaf weeds at 5-30 g/ha and shows high safety in crop rotation of rape or beans because the introduction of the methyl group at the ureido-nitrogen atom promotes rapid decomposition in soil. Triflurosulfuron-methyl was DuPont's first sugar beet herbicide

with post-emergence application and was launched in 1993. It controls annual and perennial broadleaf weeds and annual grasses such as catchweed bedstraw, slender amaranth, black nightshade, prostrate knotweed, wild mustard, salt-marsh aster, and water foxtail at rates of 10–25 g/ha in two applications. AgrEvo launched a new sulfonylurea herbicide, iodosulfuron-methyl-sodium for use on European cereals in 1999. It is effective against grass weeds including blackgrass, ryegrass and meadow grass and has a wide spectrum of broadleaf weeds by post-emergence application.

The first sulfonylurea with a pyrimidine ring was sulfometuron-methyl and its first registration was approved in 1985. It has been used in non-crop fields and grass fields, and exhibits superior efficacy at 70–840 g/ha against grass weeds, especially johnsongrass and broadleaf weeds. Structural modifications at the pyrimidine ring of sulfometuron-methyl led to chlorimuron-ethyl, which has dramatically improved the crop safety. It is used as a post-emergence herbicide in soybeans and controls common cocklebur, slender amaranth and morningglory at rates of 9–13 g/ha. Moreover, chlorimuron-ethyl has been used in combination with metribuzin as a pre-emergence herbicide.

Introduction of a difluoromethoxy group at the pyrimidine ring gives good selectivity for crops. For example, primisulfuron-methyl is a post-emergence herbicide that controls grass weeds such as johnsongrass and quackgrass as well as broad leaf weeds in maize at 20–40 g/ha. Application of less than 20 g/ha has no influence on crop rotations. Oxasulfuron is a post-emergence herbicide that controls a range of broadleaf and grass weeds such as velvetleaf, common cocklebur, common purslane, common ragweed, barnyardgrass, morningglory and johnsongrass at application rates of 45–80 g/ha in soybeans. Foramsulfuron and mesosulfuron, having additional substituents at the benzene rings, are under development.

Replacements of the usual benzene rings against hetero rings such as pyridine, thiophene, pyrazole or imidazole produced a new class of sulfonylurea herbicides. Nicosulfuron is the first example. It can control annual and perennial grass weeds such as barnyardgrass, fall panicum, quackgrass and johnsongrass as well as broadleaf weeds at 40–60 g/ha. Rimsulfuron was commercialized as a post-emergence herbicide. It exhibits strong herbicidal activity against quackgrass, johnsongrass, *Breea setosa*, purple nutsedge and atrazine-resistant broadleaf weeds at the extremely low rates of 5–15 g/ha. Green foxtail, *Panicum bisulcatum*, and southern crabgrass are sensitive for rimsulfuron. Also, it is used as a post-emergence herbicide in potato fields. Flazasulfuron is a pre- or a post-emergence herbicide active on broadleaf and grass weeds including umbrellaplant at 25–100 g/ha in sugarcane. It is also useful as a turf herbicide. Trifloxysulfuron is now under development as a cereal herbicide by Syngenta. Flupyralsulfuron-methyl-sodium, with a trifluoromethyl group at 6-position on the pyridine ring, controls annual grass weeds such as blackgrass and broadleaf weeds in cereals at a rate of 10 g/ha.

DuPont launched thifensulfuron-methyl in 1988. It is positioned as the first sulfonylurea herbicide with a five-membered heterocycle instead of the

phenyl group and controls important broadleaf weeds and *Apera spica-venti* by post-emergence application to wheat or barley at 17–35 g/ha. Nissan's pyrazosulfuron-ethyl with a pyrazole ring has been developed as a pre- or post-emergence herbicide to control annual and perennial grass weeds and many broadleaf weeds in direct-sown and transplanted rice at 14–30 g/ha. In particular, it exhibits good efficacy against *Eleocharis kuroguwai*, *Cyperus serotinus*, arrowhead, *Sagittaria pygmaea*, *Oenanthe javanica* and *Potamogeton distictus* in rice fields. Halosulfuron-methyl is selective for corn, sugarcane and turf, and can be used for controlling velvetleaf, common cocklebur and purple nutsedges with pre- or post-emergence application of 70–140 and 18–35 g/ha, respectively. DuPont's rice herbicide, azimsulfuron, was first launched in Malaysia in 1996. It controls grass weeds such as *Cyperus serotinus* and *Eleocharis kuroguwai* at the rates of 8–20 g/ha. Azimsulfuron is much more active than DuPont's older rice herbicide, bensulfuron-methyl; however, the activity against broadleaf weeds is weaker. Takeda developed two sulfonylurea herbicides with imidazopyridine rings, namely, imazosulfuron and sulfosulfuron. The former was first launched in 1993 in Japan. It controls annual and perennial broadleaf weeds, except for barnyardgrass in rice, and several combination products are now available. The latter is a post-emergence herbicide for use in wheat. It controls some grass weeds and many broadleaf weeds at rates as low as 10–30 g/ha. It is recommended for use at 27 g/ha to control wild oat, redroot pigweed, chickweed, wild mustard and stinkgrass. It also suppresses green foxtail, quackgrass and dandelion.

In the aforementioned sulfonylurea herbicides, the arylsulfonyl moiety (Aryl-SO₂) is a common structure, which is important in providing strong herbicidal activity against a wide range of weeds. In the course of structural modifications of this moiety, it was shown that an aryl-X-SO₂- moiety (X = CH₃, O or NH) was remarkably effective for increasing crop safety even at the sacrifice of powerful activity against weeds. Benzyl-modified sulfonylurea, bensulfuron-methyl is a useful rice herbicide that controls broadleaf weeds and umbrellaplant except for barnyardgrass at rates of 20–100 g/ha with pre- or post-emergence application. Cyclosulfamuron, decorated with a substituted anilino group at the sulfonylurea moiety, was launched by the American Cyanamid Comp. (ACC) group in 1997. It controls annual and perennial broadleaf weeds at application rates of 25–60 g/ha in the paddy field. Cyclosulfamuron is also active on catchweed bedstraw, wild chamomile, Persian speedwell and wild mustard, and can be applied pre- and post-emergence in autumn wheat and post-emergence in spring wheat. The development, however, has been discontinued. Ethoxysulfuron was first developed as a rice herbicide and then it was recognized as a pre- or post-emergence herbicide in small-grain cereals to control *Cyperus* sp. and clavers. It shows excellent activity against important broadleaf weeds at 10–120 g/ha in rice.

Amidosulfuron has a unique chemical structure in the sulfonylurea classes, because it includes an *N*-methyl-*N*-methylsulfonylamino group instead of

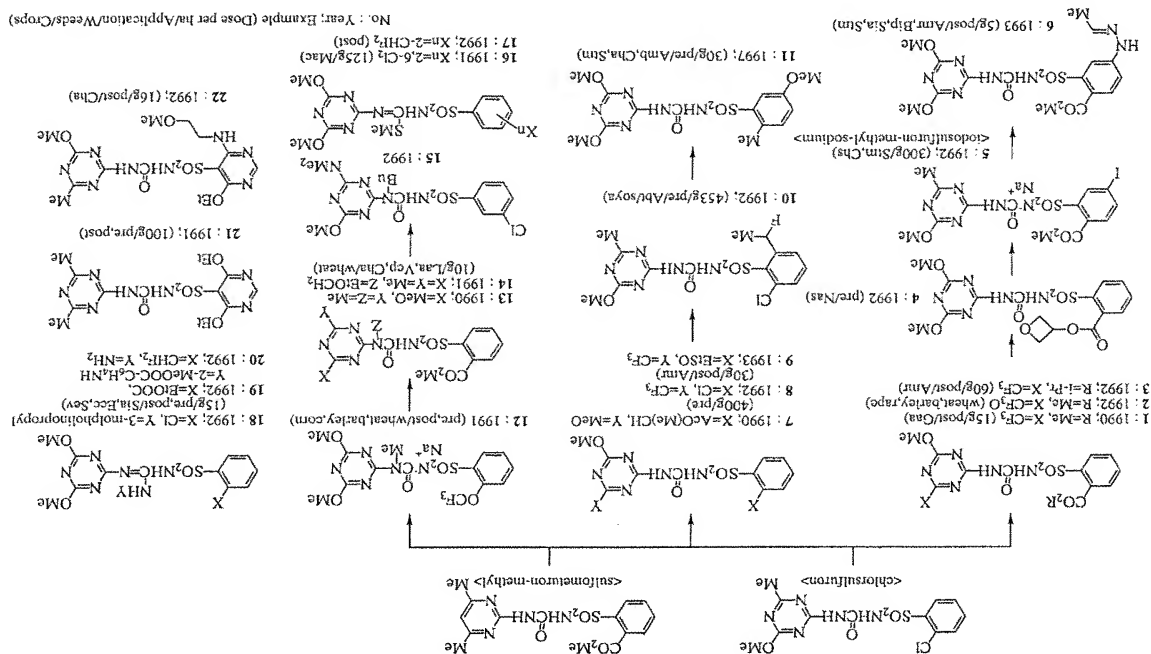
the usual aryl group at the sulfonylurea moiety. It was launched as a post-emergence herbicide by Hoechst in 1990. The active ingredient controls important broadleaf weeds including wild mustard and shepherd's purse in wheat and barley at rates of 15–60 g/ha.

10.2.1.2 Structural Evolution of Sulfonylurea Acetolactate Synthase Inhibitors

Structural modifications of triazine and pyrimidine sulfonylureas disclosed since 1990 are chronologically demonstrated in Figs. 1 and 2, respectively. With regard to the substituents at *ortho*-position of the benzene ring, slightly bulky and hydrophobic forms are essential for potent herbicidal activity. Almost all sulfonylureas cited in these figures are substituted by alkoxy-carbonyl [1–6, 13, 14, 19, 23–44], sulfonyl [9, 47, 48, 52], fluorinated alkyl [10, 17, 54, 58], trifluoromethoxy [12, 63], alkylthio groups [46, 51] or a chlorine atom [10, 16, 18, 62] at *ortho*-position. Additional substitution at the benzene ring often seems to improve herbicidal activity and crop safety. Sulfonylureas, for example triflurosulfuron-methyl with *ortho*-disubstituted phenyl rings, tend to be highly active and several compounds [10, 16, 42, 43, 62] have been produced since 1990. Moreover, sulfonylureas bearing *ortho*- and *meta*-disubstituted phenyl rings keep strong activity, although it depends on the substituent at *meta*-position. Especially, sulfonylureas [6, 11, 28–32, 34–39, 51, 53] with 2,5-disubstituted phenyl rings have been studied, and iodosulfuron-methyl-sodium [5], mesosulfuron [33] and foramsulfuron [45] are under development. Also, sulfonylureas with a 2,3-disubstituted phenyl ring have been continued [40, 41, 44].

In the course of optimization of substituents at 1,3,5-triazine and pyrimidine rings, introduction of methoxy groups at the 4- and 6-positions gave good results. Sulfonylureas with the 4,6-dimethoxy-1,3,5-triazine or 4,6-dimethoxypyrimidine ring were easily decomposed, so that carryover, a serious problem in crop rotation, was overcome. Further structural modifications are observed in the investigations of some sulfonylureas [12–20], of which urea moieties are modified with a methyl, ethoxymethyl, or butyl and other substituents. Additionally, an amidine or guanidine moiety is introduced as a mimic of the urea group. Especially sulfonylguanidine is a prototype lead compound for triazolopyrimidine ALS inhibitors mentioned later.

Structural evolution of pyridyl-sulfonylureas is chronologically depicted in Fig. 3. Practical pyridyl-sulfonylureas, namely, flazasulfuron, rimsulfuron, nicosulfuron and flupyrasulfuron-methyl-sodium have electron-withdrawing groups such as trifluoromethyl, ethanesulfonyl and dimethylcarbamoyl groups at the neighboring position of the sulfonyl group at the pyridine ring. Pyridyl-sulfonylureas proposed in the early 1990s possess electron-donating groups such as amino [76–82], alkoxy [88–93] and substituted alkyl groups [94, 95]. Alternatively, new pyridyl-sulfonylureas [83–87] with substituted amino groups only at 6-position of the pyridine ring have been suggested.



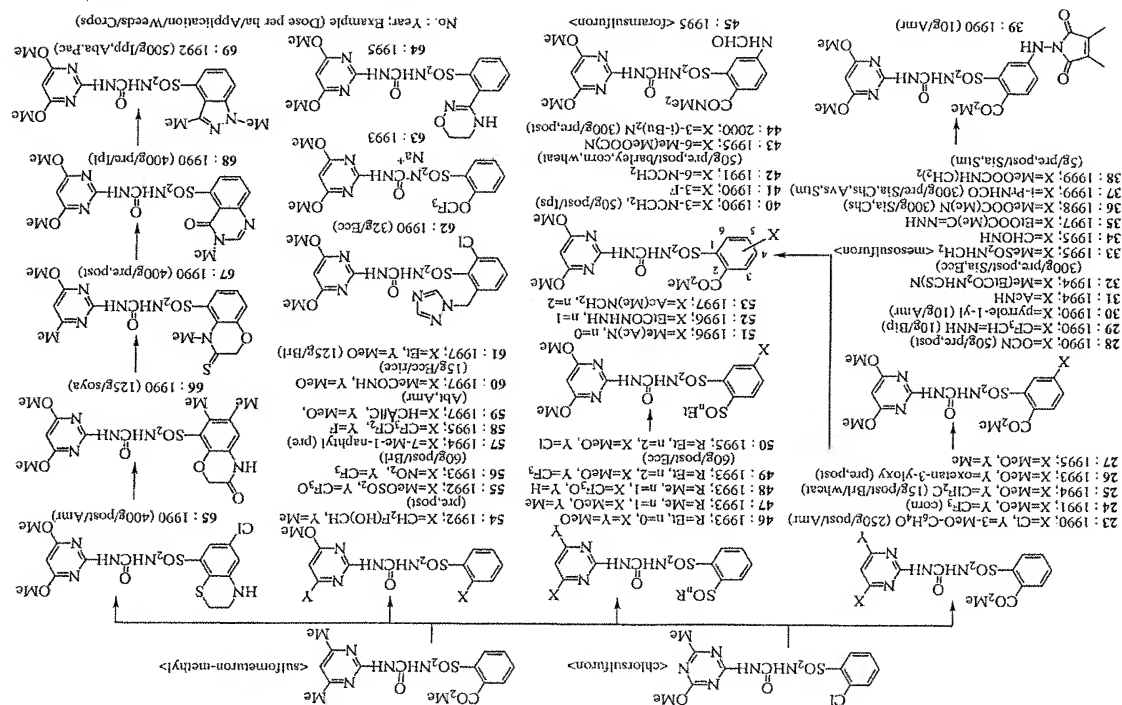


Fig. 2. Structural evolution of sulfonyleurea ALS inhibitors with pyrimidine ring since 1990

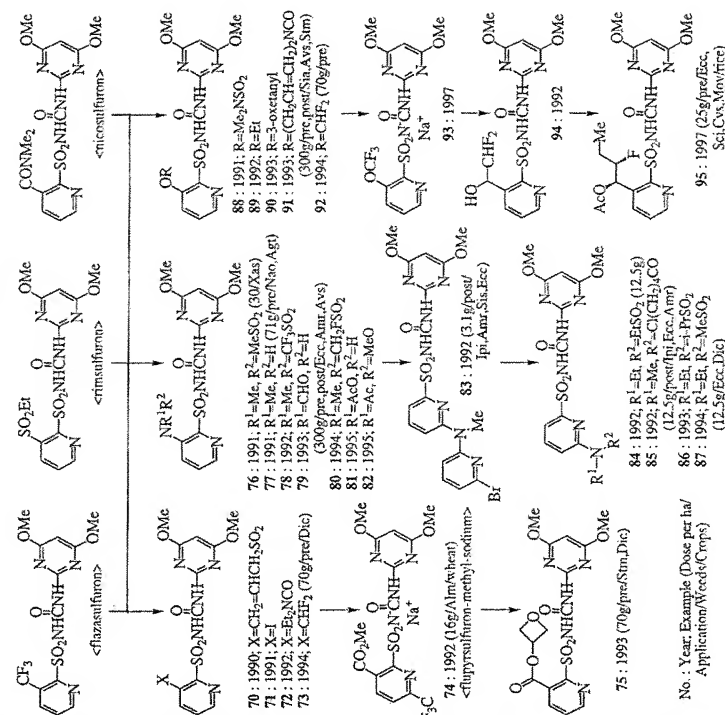
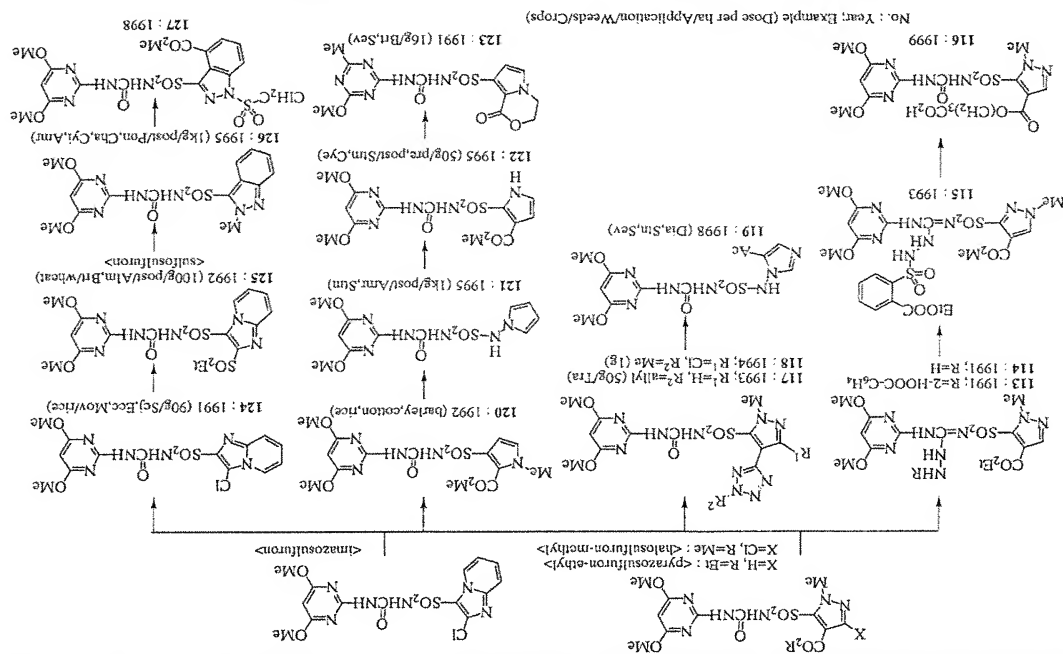
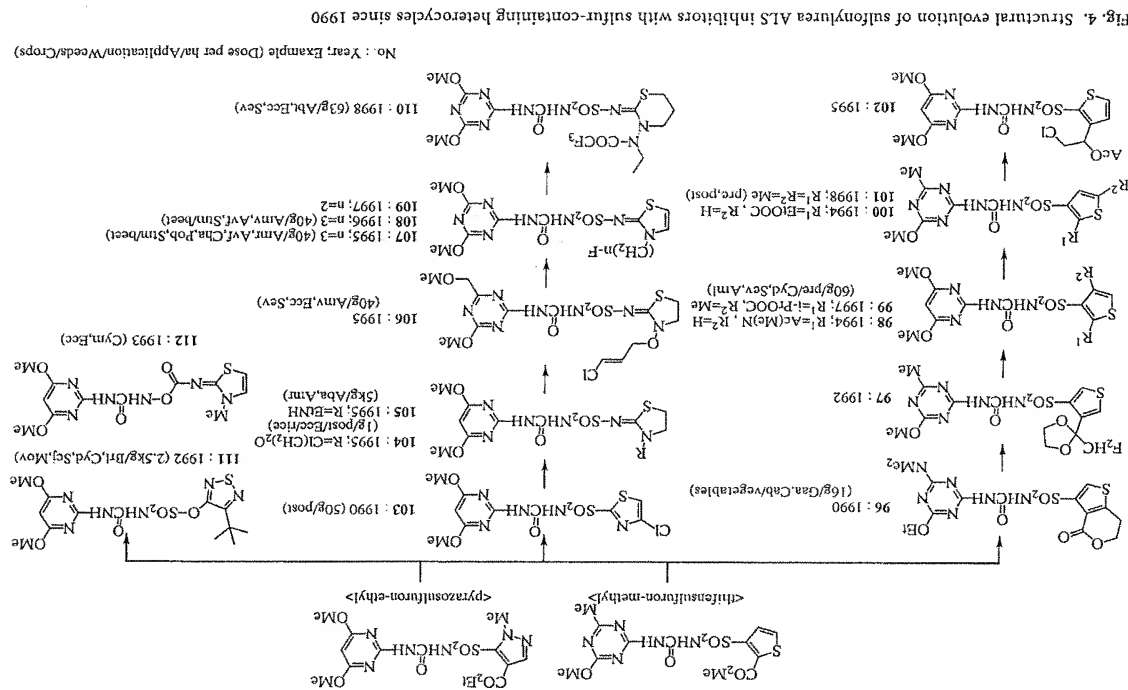


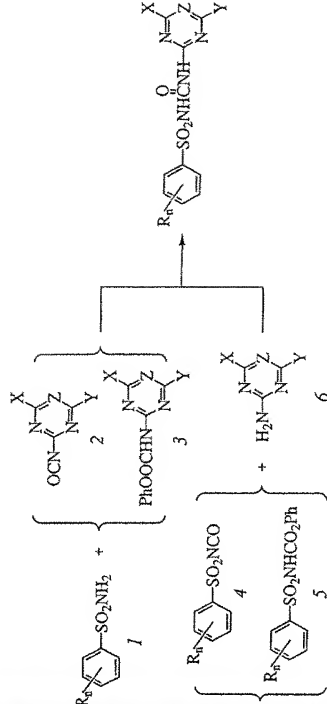
Fig. 3. Structural evolution of pyridylsulfonurea ALS inhibitors since 1990

Various kinds of sulfonyleureas with five-membered heterocycles have been aggressively developed, as shown in Fig. 4. Thifensulfuron-methyl was the first sulfonyleurea herbicide having a thiophen-3-yl group. Other sulfur-containing heterocycles such as thiazole and thiadiazole rings have been proposed since the 1990s.

Structural modifications of sulfonylureas with nitrogen-containing heterocycles such as pyrrole and pyrazole rings are shown chronologically in Fig. 5. Pyrazol-sulfuron-ethyl and halosulfuron-methyl are leading compounds for these sulfonylureas. Additionally, sulfonylureas with bicyclic heterocycles such as imidazopyridine [125] and benzopyrazole [126] have been studied continuously. Among them, imazosulfuron and sulfosulfuron are practical A.I.S. inhibitors developed by Takeda.

Other sulfonyleureas possessing substituted benzyl, sulfonamido, anilino and phenoxy groups are depicted in Fig. 6. In spite of good biological properties investigations of almost all derivatives have been discontinued.





Scheme 1. General synthetic routes for sulfonylurea moiety

10.2.1.3

Major Synthetic Routes for Sulfonylureas

There are generally two methods for preparing sulfonylurea (-SO₂NHCONH-) herbicides as shown in Scheme 1. One is the reaction of arylsulfonamides (1) with isocyanates (2) or phenyl carbamates (3), the other one is the reaction of arylsulfonyl isocyanates (4) or phenyl *N*-phenylsulfonyl carbamates (5) with arylamine (6). Major synthetic pathways for modern sulfonylurea ALS inhibitors are described briefly below.

The synthetic route for chlorsulfuron is shown in Scheme 2. Here, the key intermediate is sulfonamide (8) that is prepared from 2-chloroaniline (7) by three subsequent steps, diazotization, chlorosulfonation and amination. Phosgenation of sulfonamide (8) is accelerated by the addition of a lower alkyl isocyanate such as butyl isocyanate to yield 2-chlorophenylsulfonyl isocyanate (9), which is condensed with 2-amino-1,3,5-triazine (10) affording chlorsulfuron.

The synthesis of flupyr-sulfuron-methyl-sodium is also depicted in Scheme 2. Cyclocondensation of 4-butoxy-3-buten-2-one (11) with ester (12) followed by bromination with phosphoryl bromide gives pyridine-3-carboxylate (13). After benzylthiolation of 13, treatments with hypochlorite and *tert*-butylamine give *N-tert*-butylpyridine-2-sulfonamide (14). Deprotection of the *tert*-butyl group by trifluoroacetic acid affords sulfonamide (15), which reacts with phenyl *N*-(4,6-dimethoxypyrimidin-2-yl)carbamate (16) to give flupyr-sulfuron-methyl-sodium.

Scheme 2 also shows the synthetic procedure for thifensulfuron-methyl. The key intermediate, methyl 3-aminothiophene-2-carboxylate (18) is easily synthesized by cycloaddition reaction with chloroacrylonitrile (17) and methyl thioglycolate. After diazotization of the amino group of (18), treatment with sulfur dioxide in the presence of copper chloride and then ammonia gas gives

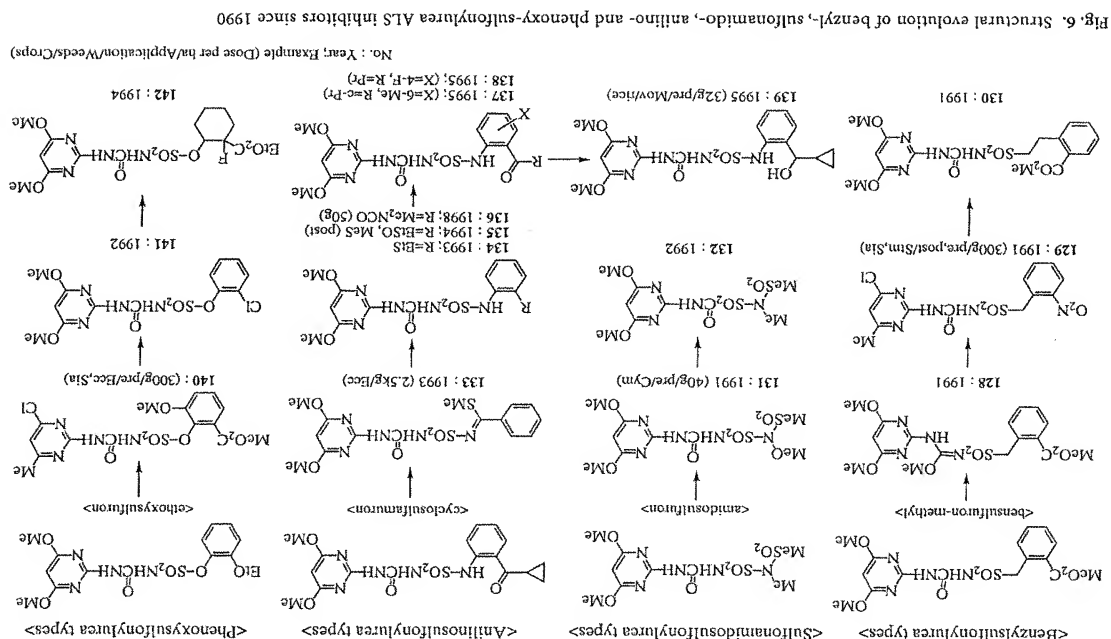
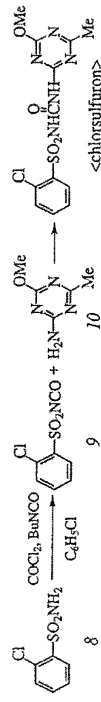
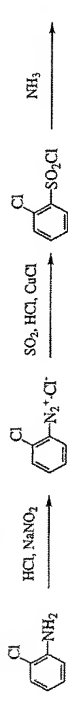
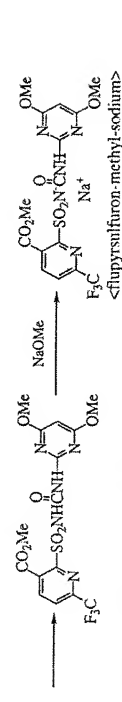
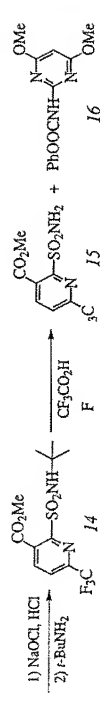
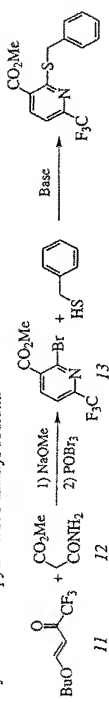


Fig. 6. Structural evolution of benzyl-, sulfonylurea, anilino- and phenoxy-sulfonylurea ALS inhibitors since 1990

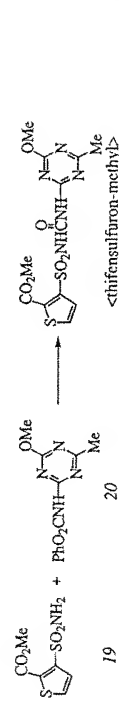
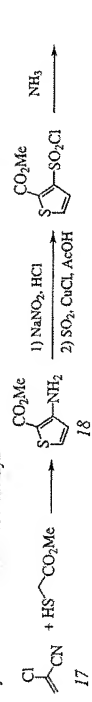
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<Synthesis of flupyr sulfuron-methyl-sodium>



<Synthesis of thifensulfuron-methyl>

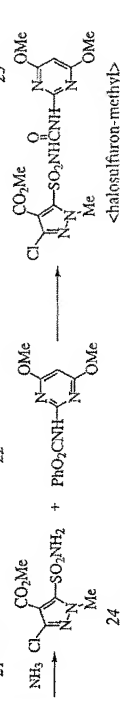
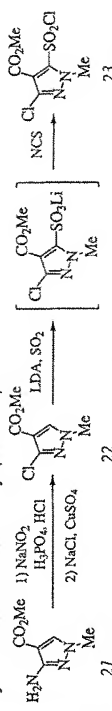


Scheme 2. Major synthetic routes for chlorsulfuron, flupyr sulfuron-methyl-sodium and thifensulfuron-methyl

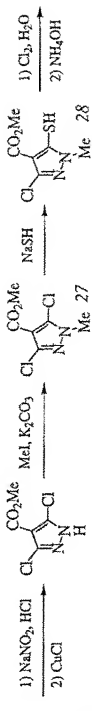
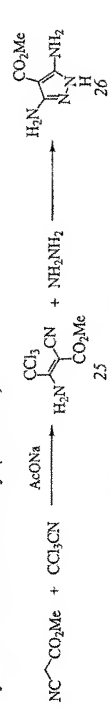
thiophene-3-sulfonamide (19). Reaction of sulfonamide (19) with phenyl N-(4-methoxy-6-methyl-1,3,5-triazin-2-yl)carbamate (20) easily proceeds to yield thifensulfuron-methyl.

For the synthesis of halosulfuron-methyl, methyl 5-aminosulfonyl-3-chloro-1-methylpyrazole-4-carboxylate (24) is an important key precursor. There are two synthetic pathways for 24 as depicted in Scheme 3. The first method is characterized by using lithium reagent. Methyl 3-amino-1-methylpyrazole-4-carboxylate (21) is selectively chlorinated at 3-position *via* diazonium salt affording 3-chloropyrazole (22). The compound (22) is treated with sulfur

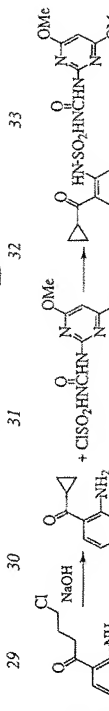
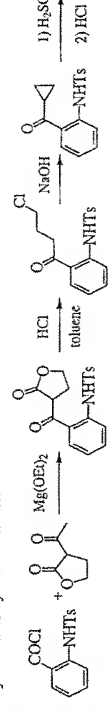
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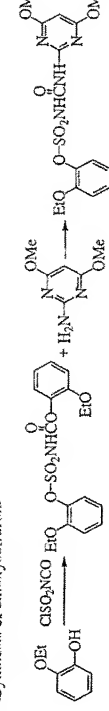
<Synthesis of halosulfuron-methyl (Method-2)>



<Synthesis of cyclosulfuron>



<Synthesis of ethoxysulfuron>



Scheme 3. Major synthetic routes for halosulfuron-methyl, cyclosulfuron and ethoxysulfuron

dioxide after lithiation by lithium diisopropylamide (LDA) and chlorinated by *N*-chlorosuccinimide (NCS) to give pyrazole (23). The key intermediate (24) is readily obtained by amination of 23. The other is the method without lithium reagent in spite of somewhat long steps. Methyl cyanoacetate condenses with trichloroacetonitrile to obtain acrylate (25). Cycloaddition reaction of 25 with hydrazine yields 3,5-diaminopyrazole-4-carboxylate (26), which is dichlorinated at the 3- and 5-positions via a diazonium salt and methylated at the 1-position. Selective thiolation at the 5-position of 27 by sodium hydrosulfide is accomplished to give methyl 3-chloro-5-mercapto-1-methylpyrazole-4-carboxylate (28), followed by treatment with a chlorine gas in water and amination subsequently giving the desired intermediate (24). Pyrazole-4-carboxylate (24) thus obtained is easily converted to halosulfuron-methyl.

Scheme 3 also shows the synthetic scheme for cyclosulfamuron including a unique method for introduction of a cyclopropylcarbonyl group. Condensation of anthraniloyl chloride (29) with 2-acetyl- γ -butyrolactone (30) in the presence of magnesium diethoxide gives anilide (31), which is heated together with concentrated hydrochloric acid in toluene to yield 4-chloro-1-(2-*N*-tosylaminophenyl)-1-butanone (32). Ring closure of 32 by treating with aqueous sodium hydroxide gives cyclopropyl ketone (33), followed by hydrolysis of the tosyl group and recyclization yielding *ortho*-aminophenyl cyclopropyl ketone (34). The ketone (34) reacts with chlorosulfonylurea (35) to yield cyclosulfamuron.

An efficient synthetic approach of ethoxysulfuron is shown in Scheme 3. It is readily synthesized by the reaction of pyrimidine (38) with 2-ethoxyphenyl-carbamate (37), which is derived by condensation of two equivalents of phenol (36) and chlorosulfonyl isocyanate.

10.2.2

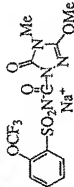
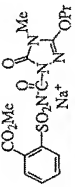
Triazolinone Acetolactate Synthase Inhibitors

10.2.2.1

Practical Triazolinone Acetolactate Synthase Inhibitors

Triazolinone herbicides are classified as second-category ALS inhibitors designed on the basis of the usual sulfonyleurea ALS inhibitors. Most triazolinone ALS inhibitors, in general, consist of substituted phenyl groups and 4,5-disubstituted triazolinone rings bridged together by a sulfonylaminocarbonyl ($-\text{SO}_2\text{NHCO}-$) moiety. Investigations have been actively continued since the 1990s and two practical herbicides, flucarbazone-sodium and procarbazone-sodium, have been commercialized and are under development (Table 2). Flucarbazone-sodium is a post-emergence cereal graminicide and controls wild oat and green foxtail at 30 g/ha. Procarbazone-sodium is being developed as a wheat herbicide.

Table 2. Practical triazolinone ALS inhibitors

Chemical structure	ISO name Code No. Company	Dose Appl. method Target crops	Patent No.
	flucarbazone-sodium BAY-MKH-6562 Bayer	30 g/ha post cereals	US5541337 EP507171
	procarbazone-sodium BAY-MKH-6561 Bayer	30-70 g/ha wheat	US5541337 US6147221 US6147222

10.2.2.2

Structural Evolution of Triazolinone Acetolactate Synthase Inhibitors

Structural modifications of orthodox triazolinone ALS inhibitors are summarized in the left column of Fig. 7. *Ortho*-positions of the benzene rings are modified by a variety of substituents, which are not always limited to electron-withdrawing groups such as the alkoxycarbonyl group. On the other hand, the substituents on the triazolinone rings are restricted to electron-donating groups except for the incipient compound [144].

10.2.2.3

Major Synthetic Routes for Triazolinone Acetolactate Synthase Inhibitors

As an example of synthetic routes for triazolinone ALS inhibitors, the major synthetic pathway of flucarbazone-sodium is illustrated in Scheme 4. Cycloaddition reaction of phenyl carbazate (39) and trimethyliminocarbonate (40) together with elimination of phenoxide gives 3-methoxytriazolinone (41), which reacts with 2-trifluoromethoxyphenylsulfonyl isocyanate (42) to yield flucarbazone-sodium (43).

10.2.3

Triazolopyrimidine Acetolactate Synthase Inhibitors

Triazolopyrimidine herbicides are grouped as the third-category ALS inhibitors that are distinguished by their triazolopyrimidine rings. Dow Agrosciences disclosed the characteristic triazolopyrimidine in the 1980s. The synthetic strategy for the construction of the triazolopyrimidine ring is of some interest to herbicide researchers. At first, 3-(arylsulfonylamino)triazolopyrimidine derivatives were designed and synthesis was attempted; however, further development was interrupted because of their low solubility. Further structural modifications resulted in inversion of $-\text{SO}_2$ and $-\text{NH}$ moieties, which improved